## REMARKS

Claims 1-38 are pending in the application. The Examiner has withdrawn claims 4-8, 15-21, 25-32, and 36-38 from consideration as being drawn to a non-elected invention. Claim 13 is cancelled without prejudice or disclaimer. Claims 12 and 23 are amended. No new matter has been added to the claims. Applicants respectfully request withdrawal of the rejections.

**Rejections under 35 U.S.C. § 112, first paragraph:**

On pages 4-6 of the Office Action, the Examiner rejects claims 1-3, 9-11, and 22-24 under enablement grounds. The examiner alleges that the specification does not enable "one skilled in the art to make and/or use the invention." More specifically the Examiner alleges that the written description "provides no correlation between hepsin gene copy number and cancer diagnosis or therapeutic efficacy" and also "provides no correlation between hepsin expression and therapeutic efficacy." Applicants respectfully disagree with the Examiner and submit that the Examiner has not established a *prima facie* case of non-enablement. Accordingly, Applicants submit that their application is in full compliance with 35 USC § 112.

It is respectfully noted that section 112 mandates that patent applications contain the "manner and process of making and using" the invention. The courts have considered applications in compliance with section 112 where the person of skill in the art can practice the invention without undue experimentation. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). The test is not whether experimentation is necessary, but whether any experimentation would be undue in view of what type and amount of experimentation is usual in that particular field. *See* MPEP §§ 2164.05 (a-b), 2164.06 (Rev. 1, February 2003). Routine design choices cannot be equated with non-enablement.

Thus, the burden to establish an enablement rejection rests with the Examiner. *See* MPEP §§ 2164.01; 2164.04 (Rev. 1, February 2003). As explained by the Federal Circuit in considering the intertwined issues of enablement and utility:

> "[I]t follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in

> the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the inventor's asserted utility. [ ] Taking these facts – the nature of the invention and the PTO's proffered evidence – into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO has not satisfied its initial burden. Accordingly, applicants should not be required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112."

See *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (emphasis added), citing *In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971).

Applicants submit that the Examiner has not met this burden, as explained below.

In the present situation, the specification clearly discloses the definitions of "amplification", "overexpression" and methods described therein to determine "gene copy number" and "expression levels" in control and test samples from a patient or a biological subject, in order to diagnose cancer or to determine therapeutic efficacy. Therefore, the skilled artisan would be able to practice the instant invention without undue experimentation.

Regarding claims 1-3 and 9-11, applicants indicate that the original specification has support for the claimed inventions. See, for example, page 15, line 29 to page 16, line 3 for a definition of amplification; and page 44, line 19 to page 45, line 4 for a description of a correlation between the presence of amplified hepsin DNA and diagnosis of a cancer, and a correlation between hepsin mRNA expression and diagnosis of a cancer.

For a description of techniques for measuring DNA copy numbers, applicants refer to page 45, lines 1-3, for example, thereby enabling a skilled artisan to estimate a hepsin gene copy number. Applicants further refer to the specification page 6, lines 29-31 to page 7, lines 1-4, lines 15-21, page 69, lines 7-9, for example, for a correlation between a gene copy number (amplification) and cancer diagnosis. Applicants also refer to specification page 56, line 13-23, for example, for a

correlation between a gene copy number and methods for monitoring efficacy of a treatment.

Applicants refer to data in Tables 1-4 regarding hepsin gene amplification and mRNA expression in tumors. For example, Table 4 shows 3% and 6% increase in hepsin gene amplification in lung and breast tumors, respectively. The data clearly indicate a correlation of hepsin gene amplification or expression and tumor occurrence, which in turn can aid in cancer diagnostics and monitoring therapeutic efficacy.

Applicants also refer to specification regarding the correlation of hepsin gene amplification and overexpression, and implication in cancer diagnosis and treatment. Specification clearly discloses (see page 43, lines 20-25) that "[T]the hepsin gene has these characteristic features of overexpression, amplification, and the correlation between the two, and these features are shared with other well studied oncogenes (Yoshimoto *et al.*, 1986, *JPN J Cancer Res,* 77(6):540-5; Knuutila *et al., Am J Pathol* 1998 152(5):1107-23). The hepsin genes are accordingly used in the present invention as a target for cancer diagnosis and treatment." Thus, the specification provides a "correlation between hepsin gene copy number and cancer diagnosis or therapeutic efficacy" and also provides a "correlation between hepsin expression and therapeutic efficacy."

Moreover, Example I (see page 64, line 22 to page 65, line 14) provides guidance regarding a correlation between hepsin gene amplification and tumor occurrence.

Regarding claims 22-24 for monitoring hepsin expression and therapeutic efficacy, applicants refer to the teaching on page 56, lines 13-30 to page 57, lines 1-2. Applicants also point out that Example VI on pages 67-68 of the specification provides an illustration of a correlation between hepsin expression and efficacy of treatment, for example, with anti-hepsin antibodies, thereby lending support to claims 22-24.

Furthermore, as the Examiner is aware, the enablement requirement is satisfied if the specification describes any method for making and using the claimed

invention that exhibits a "reasonable correlation" to the breadth of the claims. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Therefore, claims 1-3, 9-11, and 22-24 are fully enabled and applicants request the Examiner to withdraw this rejection.

**Rejections under 35 U.S.C. § 102(b):**

On pages 6-7 of the Office Action, the Examiner rejects claims 12-14 and 33-35 under 35 USC § 102(b) as allegedly being anticipated by Tanimoto *et al.* and Zacharski *et al.*, respectively.

The Examiner believes that Tanimoto *et al.* "disclose the identification of overexpressed hepsin in ovarian carcinomas", and thus "anticipate claims 12-14."

Applicants respectfully disagree with the Examiner. In order to reject a claim under 35 USC § 102, the examiner must demonstrate that each and every claim limitation is contained in a single prior art reference. See Scripps Clinic & Research Foundation v. Genentech, Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 90 (Fed. Cir. 1986); see also MPEP § 2131. Claim limitations are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. See MPEP §§ 707.07(g); 2111.01. Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. See In re Zletz, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111.

Without acquiescing to the propriety of the rejection of the claims 12-14, Applicants note that claim 12 has been amended and claim 13 has been canceled. Applicants assert that Tanimoto *et al.* do not describe the claimed methods for determining cancer by measuring hepsin gene expression level. Tanimoto *et al.* do not describe any evidence that: (i) hepsin is overexpressed in breast or lung tumor tissues, for example, (ii) hepsin is directly implicated in breast or lung tumorigenesis and cancer progression or (iii) hepsin provides opportunities for diagnostic utilities. Therefore, Tanimoto *et al.* do not anticipate the invention according to claims 12 and 14 of the instant invention.

The Examiner further states that Zacharski *et al.* "disclose immunohistochemical techniques ... to study hepsin expression", and thus "anticipate claims 33-35." Again, applicants disagree with the Examiner. Applicants submit that Zacharsky *et al.* used immunohistochemical techniques using purified polyclonal monospecific anti-hepsin antibodies to study hepsin expression. However, Zacharski does not disclose a method for diagnosing a cancer in a mammal by detecting hepsin protein expression nor does Zacharski suggest that hepsin is amplified or overexpressed in tumor lines compared to normal cells. Therefore, Zacharski *et al.* do not anticipate the invention according to claims 33-35 of the current invention.

Withdrawal of the rejections is therefore requested.

## CONCLUSION

In view of this Amendment and applicants' remarks above, applicants respectfully submit that claims 1-3, 9-12, 14, 22-24, and 33-35 are allowable, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,

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